IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

AF #18
GP 1623
4-21-00
Done

In re Patent Application of

Reid W. von Borstel, et al

Serial No. 08/463,740

Filed: June 5, 1995

Atty Dkt.: 1331-143
C# M#

Group Art Unit: 1623

Examiner: Kunz

Date: April 17, 2000

Title: PYRIMIDINE NUCLEOTIDE PRECURSORS FOR TREATMENT OF SYSTEMIC INFLAMMATION AND INFLAMMATORY HEPATITIS

Honorable Commissioner for Patents and Trademarks
Washington, DC 20231

Sir:

☐ **NOTICE OF APPEAL**
Applicant hereby appeals to the Board of Appeals from the decision dated _____ of the Examiner twice/finally rejecting claims _____ ($ 300.00) — $ 0.00

☒ An appeal **BRIEF** is attached in triplicate in the pending appeal of the above-identified application ($ 300.00) — $ 300.00

☐ An **ORAL HEARING** is requested under Rule 194 ($ 260.00) (due within two months after Examiner's Answer) — $ 0.00

☐ Credit for fees paid in prior appeal without decision on merits — -$ (0.00)

☐ A reply brief is attached in triplicate under Rule 193(b) — **(no fee)**

☒ Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) **($110.00/1 month**; $380.00/2 months; **$870.00/3 months**; $1,360.00/4 months) — $ 1850.00

SUBTOTAL $ 2150.00

☒ Applicant is a "small entity"; enter ½ of subtotal and subtract — -$(1075.00)
☐ "small entity" statement attached

SUBTOTAL $ 1075.00

Less month extension previously paid on — -$(0.00)

TOTAL FEE ENCLOSED $ 1075.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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By Atty: Leonard C. Mitchard, Reg. No. 29,009

Signature: _____

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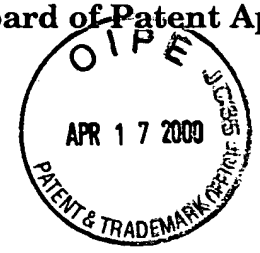

In re Patent Application of

von BORSTEL et al

Serial No. **08/463,740**

Filed: **June 5, 1995**

Atty. Ref.: **1331-143**

Group: **1623**

Examiner: **Kunz, G.**

For: **PYRIMIDINE NUCLEOTIDE PRECURSORS FOR TREATMENT OF SYSTEMIC INFLAMMATION AND INFLAMMATORY HEPATITIS**

* *

April 17, 2000

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

APPEAL BRIEF

Sir:

Applicant hereby appeals the Final Rejection of March 17, 1999, Paper No. 16. A Notice of Appeal was filed on September 17, 1999, along with a three month extension request.

REAL PARTY IN INTEREST

The real party in interest is Pro-Neuron, Inc., a corporation of the country of the USA.

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RELATED APPEALS AND INTERFERENCES

The appellant, the undersigned, and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 41 and 58-67 are pending. Claims 1-40 and 42-57 are canceled. Claims 41 and 58-67 are rejected, and are the subject of the present appeal.

STATUS OF AMENDMENTS

No amendments have been filed since the date of the Final Rejection.

SUMMARY OF INVENTION

The invention relates to generally to pyrimidine nucleotide precursors, including acyl derivatives of cytidine, uridine and orotic acid, and to the prophylactic and therapeutic uses of these compounds (page 1, beginning at line 12). These compounds of capable of enhancing resistance to an animal or bacterial endotoxin and other inflammatory stimuli, and inflammatory mediators (page 1, lines 17-19). As noted on page 2, beginning at line 2, sepsis is a consequence of serious infection by bacteria, fungi or viruses.

Sepsis accounts for tens of thousands of deaths in the United States every year, and it is a leading cause of death of patients in surgical intensive care units. Sepsis is an inflammatory disorder in which endogenous cytokines and other bioactive molecules, produced or released in response to an inflammatory stimulus such as bacterial endotoxin (a component of the cell wall of gram-negative bacteria), cause various symptoms, including fever, neutropenia, blood coagulation disorders, hypotension, shock, and organ damage (page 2, lines 7-13).

Sepsis is one example of a broader class of disease called the "Systemic Inflammatory Response Syndrome" (SIRS). This is an organism's reaction to inflammatory stimuli such as endotoxin (which can be present in the bloodstream without bacteremia, for example, due to leakage of endotoxin from gram-negative bacteria into the circulation from a localized infection or from the intestine. SIRS can also be triggered by gram-positive bacteria, fungi and viruses, and can also be a consequence of auto-immune disorders or administration of therapeutic inflammatory cytokines (page 2, third complete paragraph).

The invention provides therapeutic and prophylactic compositions which are effective in improving survival and in preventing tissue damage from SIRS, including sepsis (page 7, last complete paragraph). In the invention as claimed, pharmaceutical compositions are provided comprising an acyl derivative of uridine,

cytidine or orotic acid and an inhibitor of uridine phosphorylase. The compositions of the invention are described in detail beginning on page 26 and extending through to page 28. A discussion of the therapeutic uses of the compounds and compositions of the invention begins at the bottom of page 28 of the application.

ISSUES

The issue for consideration by the Board is whether the claimed compositions are obvious over von Borstel when taken in view of Chu et al. This is the sole issue in the case.

GROUPING OF CLAIMS

Claims 41 and 58-67are the subject of the present appeal. Those claims stand or fall depending on the outcome of the Board's Decision

ARGUMENT

(1) The Examiner's Rejection

The sole rejection in the case is that of alleged obviousness of Claims 41 and 58 - 67 under 35 USC 103 over von Borstel et al. in view of Chu et al. for the reasons already of record on pages 2 - 3 of the Office action mailed April 2, 1996. The Examiner notes that the claims are directed to compositions comprising acylated uridine or acylated cytidine and a uridine phosphorylase inhibitor. The Examiner then asserts:

"Von Borstel et al. discloses compositions comprising acylated uridine or cytidine for elevating blood and tissue levels of free uridine for the treatment of a wide variety of diseases. Von Borstel et al. does not mention uridine phosphorylase inhibitors. However, the Chu et al. reference does teach the use of uridine phosphorylase inhibitors to potentiate the chemotherapeutic effect of pyrimidine nucleoside analogs, such as 5-fluorouridine, by preventing the degradation of said nucleoside analog. The examiner emphasizes that the artisan upon seeing the disclosure of Chu et al. concerning the uridine phosphorylase inhibitors would immediately recognize that such inhibitors would, by definition, increase the blood and tissue levels of free uridine by preventing its degradation. Therefore, Von Borstel et al. and Chu et al. each disclose a different method for elevating the blood and tissue levels of free uridine. Consequently, the person of ordinary skill in the art at the time of the invention would have found it obvious to combine acylated uridine (taught by Von Borstel et al.) with uridine phosphorylase inhibitors (taught by Chu et al.) in order to further elevate the blood and tissue levels of free uridine in order to treat the disorders identified by Von Borstel et al. as responsive to exogenous uridine. Since the availability of uridine is apparently a limiting nutritional factor in cellular repair, then one

would reasonably expect that optimizing that concentration of free uridine would enhance cellular repair and replication."

In response to the arguments previously presented, the Examiner asserts:

"The applicant argues that there is no motivation to combine the two different methods and compounds for increasing blood and tissue uridine disclosed by each reference. This argument has been fully considered but is not deemed persuasive. Von Borstel et al. teaches that the art recognized goal for treating a variety of diseases or disorders is to increase the free uridine concentration in the blood and tissue with a minimum of side effects. Clearly, the reasonable artisan would have every reason to use a combined modality of treatment in order to achieve the highest safe levels of free uridine, and thereby the highest therapeutic benefits."

(2) **Appellants' Rebuttal**

Claims 41 and 58-67 stand rejected under 35 U.S.C. • 103 as being unpatentable over von Borstel et al in view of Chu et al. Reversal of the rejection is respectfully requested.

Claim 41 is directed to a composition comprising (a) an acyl derivative of uridine, cytidine or orotic acid, and (b) an inhibitor of uridine phosphorylase. The remaining claims in the case (Claims 58-67) are composition claims which are dependent, either directly or indirectly, on Claim 41.

The claims in this application are not rendered obvious by the combined teachings of von Borstel et al (WO 89/03837) when taken in view of Chu et al (U.S. Patent No. 4,613,604). Reversal of the rejection is accordingly respectfully requested.

Von Borstel describes acylated derivatives of uridine and cytidine. As conceded by the Examiner, there is no disclosure or suggestion in that reference of compositions comprising an acyl derivative of uridine, cytidine or orotic acid and an inhibitor of uridine phosphorylase.

Chu et al., on the other hand, relates principally to the treatment of cancer, and has nothing to do with compositions suitable for use in the treatment of inflammatory disorders. Chu et al describes the use of hydroxymethyl derivatives of 5-benzylacyclouridine and 5-benzoyloxybenzylacyclouridine in the potentiation of pyrimidine nucleosides, such as 5-fluoro-2'-deoxyuridine (FdUrd), in cancer

chemotherapy by way of uridine phosphorylase inhibition. The focus of Chu et al is to **prevent the cleavage of the nucleoside analog to a less effective material**, and **not** to elevate uridine levels. As noted at column 1, lines 15 through 17 of Chu et al:

> "The efficacy of the chemotherapeutic agent FdUrd is limited by its **cleavage** the less effective base 5-fluorouracil (FUra)." (Emphasis added)

Chu et a further states at column 3, line 67:

> "A specific object of the present invention is to provide novel uridine phosphorylase inhibitors which reduce **phosphorolytic degradation** of FdUrd to the less active FUra in tumor cells." (Emphasis added)

The Examiner takes the position that there would be motivation in the mind of one of ordinary skill to combine these disclosures to arrive at the present allegation of obviousness. It not seen how such motivation could possibly arise in the mind of a person of ordinary skill in view of the disclosures of the cited references. Chu et al relates to the treatment of cancer and is premised on the prevention of degradation of **FdUrd to the less active FUra** in tumor cells. Von Borstel describes **acylated** derivatives of uridine and cytidine, and provides no suggestion of compositions comprising an **acyl** derivative of uridine, cytidine or orotic acid and an inhibitor of uridine phosphorylase. It is believed therefore that a

person of ordinary skill would not have been motivated to combine the disclosures von Borstel et al and Chu et al to arrive at the compositions as claimed in the present application. Absent any such motivation to combine these disclosures, it is clear that a *prima facie* case of obviousness has not been established in this case.

For the above reasons, reversal of the obviousness rejection is believed to be in order. Such action is respectfully requested.

CONCLUSION

In conclusion it is believed that the present application is in clear condition for allowance. Reversal of the Final Rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

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APPENDIX

The claims on appeal are Claims 41 and 58-67. These read as follows.

41. A composition comprising:

a) an acyl derivative of uridine, cytidine or orotic acid,

and;

b) an inhibitor of uridine phosphorylase.

58. A composition as in claim 41 wherein said acyl derivative is an acyl derivative of uridine.

59. A composition as in claim 41 wherein said acyl derivative is an acyl derivative of cytidine.

60. A composition as in claim 41 wherein said acyl derivative is an acyl derivative of orotic acid.

61. A composition as in claim 58 wherein said acyl derivative of uridine is a fatty acid ester of uridine having 2-6 carbon atoms.

62. A composition as in claim 59 wherein said acyl derivative of cytidine is a fatty acid ester of cytidine having 2-6 carbon atoms.

63. A composition as in claim 58 wherein said acyl derivative of uridine is triacetyl uridine.

64. A composition as in claim 59 wherein said acyl derivative of cytidine is triacetyl cytidine.

65. A composition as in claim 41 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of 5-benzyl barbiturate or 5-benzylidene barbiturate derivatives, 2,2'-anhydro-5-ethyluridine, 5-ethyl-2-deoxyuridine and acyclouridine compounds.

66. A composition as in claim 65 wherein said 5-denzylidene barbiturate is selected from the group consisting of 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, 5-benzyloxybenzylacetyl-2-[(1-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

67. A composition as in claim 65 wherein said acyclouridine compound is a 5-benzylsubstituted acyclouridine congener selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclouridine, aminomethyl-benzylacyclouridine, aminomethylbenzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, and hydroxymethyl-benzyloxybenzylacyclouridine.